placing the distal opening in proximity to the cell; and

causing an electrical signal to pass through the conductive fluid and the cell wherein the substance passes through the distal opening and enters the cell.

REMARKS

In response to the Office Action of February 15, 2002, Applicants have amended the claims which, when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The drawings have been objected to under 37 C.F.R.§ 1.83(a) as allegedly not showing every feature of the invention specified in the claims. The Examiner has therefore requested that Applicants furnish a drawing under 37 C.F.R. § 1.81 showing the electroporation assembly or else cancel such features from the claims. In response to the objection, Applicants submit herewith, Figures 5, 6A, and 6B which illustrate the electrophoresis assembly of the present invention. Applicants have also amended the Brief Description of the Drawings, to include a description of Figures 5, 6A, and 6B. Support for the description of Figures 5, 6A, and 6B may be found throughout the specification as originally filed, e.g., pages 6-9. In view of newly submitted Figures 5, 6A, and 6B, and the amendment to the Brief Description of the Figures, withdrawal of the objection to the drawings is warranted.

Claim 5 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that at the time the application was filed, the inventors were in possession of the invention. It is the Examiner's position that "tissue support" was not thoroughly described in the claims, specification, or drawings. Applicants respectfully traverse

the rejection of Claim 5 under 35 U.S.C. §112, first paragraph, and submit the following. Page 8, lines 9 through 15 disclose:

The distance between the distal opening of the container and the second electrode should be wide enough to accommodate a single cell, tissue sample, or a living organism. It is contemplated that a tissue or cell support made of a relatively conducive material can be interposed between the distal opening and the second electrode. Alternatively, the cell of the sample can be supported by the second electrode itself, e.g., a ground plate. In another embodiment, the tissue sample can be stretched across the locus of the distal opening and in this manner be located between the first and second electrodes.

Conductive materials are described on page 7, lines 12-14, as including materials such as silver, platinum, gold, aluminum, stainless steel, titanium, copper, carbon, alloys of the aforementioned materials and the like, which alloys are well known in the art. Applicants respectfully submit that one skilled in the art, having the specification of the present application in hand, would understand that the term "tissue or cell support" is exactly that-- a structure which supports the tissue or cell *interposed between the distal opening and the second electrode,* and which is made of a relatively conducive material. As an example, the specification teaches that the second electrode, e.g., a ground plate, can serve as a tissue or cell support. Withdrawal of the rejection of Claim 5 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Claims 4 and 12 appear to have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner specifically objects to the phrase "diameter less than the diameter of a target cell" as recited in Claims 4 and 12, stating that the phrase "is a relative term which renders the claim indefinite." According to the Examiner, "[t]here has not been provided a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." February 15, 2002 Office Action, page 3, lines 1-4.

In determining whether claims comply with the second paragraph of section 112, a determination is first made as to whether the claims "set out and circumscribe a particular area with a reasonable degree of precision and particularity." *In re Moore*, 39 F.2d 1232, 169 USPQ 236 (CCPA 1971). The claims should not be considered in a vacuum, "but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *Id.* In examining the claims for compliance with section 112, second paragraph, all limitations should be given effect. *In re Geerdes*, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

Applicants respectfully submit that one possessing the ordinary level of skill in the art and having the teachings of the prior art as well as the specification of the present application in hand, would reasonably understand Claims 4 and 12 to set out and circumscribe the diameter of the distal opening of the container as having a diameter smaller than a target cell i.e., a cell being electroporated using the container. One skilled in the art would understand that the size of the distal opening could be changed based on the cell type being electroporated. The skilled artisan would have such an understanding based on (1) the prior art, which teaches the diameters of different cell types, and (2) the specification, which teaches the preferred relationship between the size of the diameter of the distal opening and a target cell diameter. *See* specification, page 6, lines 25-27. *See also* specification, page 13, where micropipettes having a diameter of 2 μm were used for electroporation of intact tadpole brain cells. Withdrawal of the rejection of Claims 4 and 12 is therefore warranted.

Claims 1-29 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Dev et al., U.S. Patent No. 5,993,434, and further in view of Weaver et al., U.S. Patent No. 5,911,223; Atkins et al., "Localized Electroporation: a Method for Targeting Expression of Genes in Avian Embryos", *BioTechniques,* Vol. 28, No. 1, (2000) , and Teruel et al. "A versatile microporation technique for the transfection of cultured CNS neurons" *J. Neuroscience Methods* 93 (1999) 37-48.

Dev et al. teach *in vivo* electroporation of DNA and other molecules using an apparatus having multiple needles. For example, the patent teaches at column 3, lines 58-61, that a plurality of needles are mounted in grooves, equally spaced around the outer surface of the needle collar, providing a circular array of equally spaced needles. Thus, the method using the apparatus of Dev et al. involves injection of DNA or a drug and electrical stimulation through multiple needles. The metal needles also function as electrodes with stimulation delivered between a central needle and the needles in a surrounding circular array. There is no teaching or suggestion in Dev et al. for a *singular* container comprising an electrode disposed therein and a second ground electrode.

Weaver et al. teach the delivery of agents by electroporation to the surface of tissues, including skin tissue. The electroporation methods taught by Weaver et al. are specifically designed to deliver agents to a large area of tissue. Material is delivered to the surface of the tissue using a relatively large electrode/reservoir device. The electrode within the reservoir (container) is a mesh, placed flat against the electrode/reservoir opening exposed to the tissue surface. There is no teaching or suggestion in Dev et al. for a thin conductive wire serving as an inter-reservoir electrode which simply has to be in contact with a conductive delivery solution.

The device taught by Weaver et al. could not be used in the methods of the present invention to deliver agents to single cells on the surface or deep within tissues.

Atkins et al. teach a method of electroporation of small populations of cells in living embryos with plasmid-borne genes. The method employs a double-barreled suction electrode, backfilled with a DNA-containing solution and driven by a conventional neurohysiological stimulator. DNA solution is placed in both barrels and electrical stimulation is delivered between the two barrel tips by wire electrodes in *each* barrel. In contrast, the electroporation assembly of the present invention has a first electrode *positioned within a singular container* and in direct electrical communication with a conductive fluid. Thus, one electrode is in contact with the delivery solution within the first container. A second electrode is placed in electrical contact with the tissue, but such contact can be in the tissue, in the culture medium, or in a saline bath and thus may be positioned some distance away from the first electrode.

The barrel tips of the electroporation device of Atkins et al. are much larger in comparison to the size of the distal tip diameter of the containers of the present invention. For example, the tip diameters disclosed in Atkins et al. are about 200-250 μm. *See* Atkins et al., page 96, column 3, lines 1-8 under "Materials and Methods". The tip diameter exemplified by the present invention is 2.0 μm. *See* Example II.

Moreover, as presently amended, Claims 1 and 9 recite in relevant part "a singular container having a distal opening". The double-barreled suction electrode of Atkins et al. should not be considered a singular container.

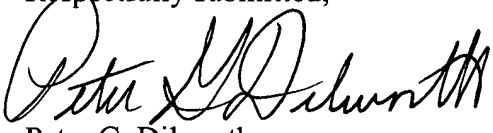
Teruel et al. teach a microporator device where solutions are delivered to cultured cells from a central injector pore. An electric field is delivered between two electrodes *positioned on either side of the injector.* In contrast, the electroporation assembly of the present invention has

a first electrode *positioned within a first container*. Thus, one electrode is in contact with the delivery solution within the first container. A second electrode is placed in electrical contact with the tissue, but such contact can be in the tissue, in the culture medium, or in a saline bath.

The present invention differs from the teachings of the prior art with respect to its novel features described above. Summarizing, these novel features include a singular container having a distal opening, the container configured to receive a conductive fluid including a substance, wherein the container has at least a portion of a first electrode disposed within the container and a second electrode is positioned in proximity to the distal opening for creating an electric field between the electrodes. Such novel features recited by the presently amended claims, allow exquisite control over the location and number of cells receiving a desired substance, allow for use at the surface of a single exposed cell or deep within tissue, and allow for use in whole live organisms. None of the cited references, taken alone or in combination, teach or suggest the novel features recited by the presently amended claims. Even if one skilled in the art was well aware of the techniques of electroporation, including the use of dyes and colored proteins as taught e.g., by Teruel et al., as well as the commonly used tools such as a pipette as taught, e.g., by Atkins et al., and even if it were obvious to modify the device and methods of Dev et al., with the specifics of Weaver et al., as the Examiner has asserted (a point on which Applicants do not agree with the Examiner), one skilled in the art would still not arrive at Applicants' invention. Withdrawal of the rejection of Claims 1-29 under 35 U.S.C. 103(a) is therefor warranted.

In view of the foregoing remarks and amendments, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Peter G. Dilworth
Reg. No. 26,450
Attorney for Applicants

DILWORTH & BARRESE
333 Earle Ovington Blvd.
Uniondale, NY 11553
(516) 228-8484
PGD/bg

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An electroporation assembly comprising:

a singular container having a distal opening, the container configured to receive a conductive fluid including a substance;

a first electrode having at least a portion configured to be disposed within the container and in direct electrical communication with the conductive fluid; and

a second electrode positioned in proximity to the distal opening for creating an electric field between the electrodes.

9. (Amended) A method for delivering a substance into a cell said method comprising:

providing a singular container having a distal opening;

placing a conductive fluid including a substance in the container;

placing the distal opening in proximity to the cell; and

causing an electrical signal to pass through the conductive fluid and the cell wherein the substance passes through the distal opening and enters the cell.